UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY, and MANULIFE INSURANCE COMPANY (f/k/a INVESTORS PARTNER INSURANCE COMPANY), Plaintiffs, vs. ABBOTT LABORATORIES, Defendant.	Civil Action No. 05-11150-DPW Hon. Judge Douglas P. Woodlock

ABBOTT'S OBJECTIONS TO THE AFFIDAVIT OF WILLIAM R. FAIRWEATHER, PHD

1. Abbott objects to paragraphs 25, 29, 41, 42 and 43 of the Affidavit of William R. Fairweather, filed January 28, 2007, on the grounds that they are untimely under Federal Rule of Civil Procedure 26(a)(2)(B) because they constitute new opinions that were not disclosed in Dr. Fairweather's expert report in this matter, entitled "Report of William Fairweather, PhD", dated January 19, 2007. A true and correct copy of Dr. Fairweather's expert report, as served on Abbott ("Fairweather Report"), is attached hereto as Exhibit A. The above-referenced paragraphs offer new opinions by Dr. Fairweather on the use of imputed data in clinical studies, the alleged reactions of the FDA to the use of such data, the ABT-594 M99-114 clinical trial protocol, and the projected statistical power of the M99-114 clinical trial based on a different "usable sample" of trial subjects than Dr. Fairweather had considered in his expert report. The

Court should exclude the above-referenced paragraphs of Dr. Fairweather's affidavit, as well as any testimony concerning the subjects set forth in those paragraphs.

The previously undisclosed new opinions in Dr. Fairweather's affidavit relate to the statistical implications of the procedure set forth in the protocol for the M99-114 clinical trial for ABT-594 for analyzing data from the subjects who enrolled in the trial, but prematurely terminated. In his expert report, Dr. Fairweather states that, out of the 269 patients enrolled in the study, the "usable sample size would be only 137 patients" who actually completed the study. Fairweather Report, p. 12. Dr. Fairweather then goes on to base his conclusions and opinions regarding the study and its statistical power on that 137 patient "usable sample". *Id.*, pp. 12-13. In his affidavit filed January 28, 2007, Dr. Fairweather for the first time offers opinions about the statistical implications of the use of a significantly larger "usable sample" of patients, based on the procedures and methodology set forth in the protocol for the M99-114 trial that he did not consider or offer opinions about before.

Pursuant to the Court's Order filed on October 25, 2007, and entered on October 29, 2007, the parties were permitted to file "Updated, Final Versions of Their Expert Reports" no later than December 1, 2007. At the Pretrial Conference on October 25, 2007, the Court made clear that the updated expert report was to contain all of the expert's opinions in a refined form, "so that, as the Court stated, the parties would know "what his last -- or her last and best offer is about testimony." Transcript, October 25, 2007 Pretrial Conference, p. 49. True and correct copies of the relevant pages of the transcript of the October 25, 2007 Pretrial Conference are attached hereto as Exhibit B. However, Hancock did not submit an updated version of the Fairweather report. Dr. Fairweather and Hancock had the opportunity to submit a revised report, but chose not to do so. Thus, pursuant to the Court's instruction at the October 25 Pretrial

Conference, Dr. Fairweather's report dated January 19, 2007 constitutes his final, "last and best offer" about his expert testimony in this matter.

Under Federal Rules of Civil Procedure 26(a)(2)(B) and 37(c)(1), as well as the Court's order of October 25, 2007, the new opinions referenced above in Dr. Fairweather's affidavit should be excluded from evidence. Under Rule 26, the expert's report must "contain a complete statement of all opinions to be expressed and the basis and reasons therefore." Fed. R. Civ. P. 26(a)(2)(B) And the Court properly exercises its "gatekeeper" function in striking expert testimony that goes beyond that disclosed in the expert's report. *See, e.g.*, *See Boardman v. National Med. Enters.*, 106 F.3d 840, 843 (8th Cir. 1997) (affirming exclusion of expert opinions not disclosed in report, but raised for first time during deposition). Hancock cannot meet its burden under Rule 37(c)(1) of showing that its violation of Rule 26(a) was either justified or harmless. Dr. Fairweather admittedly reviewed the M99-114 protocol before submitting his expert report. He either knew or should have known about the facts and issues underlying his new opinions before submitting his expert report, including the issues of imputed data and usable sample size under the procedure and methodology set forth in the clinical protocol. He simply chose not to address them in his expert report. The sanction of preclusion of the opinions of Dr. Fairweather in the paragraphs of his affidavit referenced above is therefore mandatory. *See Silong v. United States,* No. CV F 06-0474 LJO DLB, 2007 WL 2712100 (E.D. Cal. Sept. 14, 2007) (entering "mandatory" exclusion order for failure to comply strictly with Rule 26 requirements).[1]

[1] For both factual and legal reasons, Hancock cannot argue that Dr. Fairweather's deposition testimony cures its failure to provide an adequate report. First, Dr. Fairweather did not, in fact, testify at his deposition to all of the previously undisclosed opinions and their bases referenced above. Second, and more importantly, the law prohibits Hancock from remedying shortcomings in their experts' reports by relying on their experts' deposition testimony. *See, e.g., Silong, 2007 WL 2712100 at *4-5; Ferriso v. Conway Organization*, 1995 WL 580197 at *3 (S.D.N.Y. Oct. 3, 1995) (rejecting argument that

2. Abbott objects to paragraphs 33, 36, 37, 38, 40, 41 and 43 of Dr. Fairweather's affidavit on the ground that Dr. Fairweather's opinions in these paragraphs as to Abbott's supposed state of mind or motives, including without limitation what Abbott and/or its employees allegedly "recognized" (par. 33), "was aware of" (par. 36), "were aware, or should have been aware" (par. 37), "should have recognized" (par. 40), "should have understood" and "knew" (par. 41), and "should have known" (par. 43) is improper, incompetent, and is inadmissible under Rule 702 of the Federal Rules of Evidence. Abbott also objects on the same grounds to Dr. Fairweather's opinions at paragraph 42 that the "FDA would have had serious questions about any statistical data. . . ."

Rule 702 permits witnesses qualified as experts to offer opinion testimony only if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case. Fed. R. Evid. 702. Under Rule 702, the trial judge "must ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable." *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 589 (1993); *see also Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 149 (1999) (extending *Daubert*'s requirements to all expert testimony). The Court should exclude an expert report that does not meet the *Daubert* standards even in a bench trial because the purpose of *Daubert* is to "assist the trier of fact to understand or determine a fact in issue" and to ensure that the "expert testimony is relevant and helpful." *See Williams v. Poulos*, 11 F.3d 271, 282 (1st Cir. 1993) (motion in limine excluding expert report

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deposition testimony served as "implicit amendment" to written expert disclosure required by Rule 26). Of course, permitting deposition testimony to supplant expert reports would eliminate any incentive for parties to comply with Rule 26(a). *See generally Ortiz v. Sociedad Espanola*, 248 F.3d 29, 35 (1st Cir. 2001) (explaining that preclusion sanction in Rule 37(c)(1) is intended to "uphold and facilitate" compliance with Rule 26(a)).

properly granted in bench trial); *Seaboard Lumber Co. v. U.S.*, 308 F.3d 1283, 1302 (Fed. Cir. 2002) ("While these concerns are of lesser import in a bench trial, where no screening of the factfinder can take place, the *Daubert* standards of relevance and reliability for scientific evidence must nevertheless be met.").

An expert may not be called to testify as to a party's state of mind -- what that party was thinking or knew or intended. *See, e.g., CMI-Trading, Inc. v. Quantum Air, Inc.*, 98 F.3d 887, 890 (6th Cir. 1996) ("The intent of the parties is an issue within the competence of the jury and expert opinion testimony will not assist the jury, within the meaning of Federal Rule of Evidence 702, in determining the factual issue of intent."). Such testimony is no more appropriate as applied to the state of mind of a corporation or its employees. *See DePaepe v. General Motors Corp.*, 141 F.3d 715, 720 (7th Cir. 1998) (holding that trial court erred by allowing expert to testify as to why General Motors had reduced the amount of padding in its automobile sun visors because expert "lacked any scientific basis for an opinion about the motives of GM's designers"); *In re Rezulin Products Liability Litig.*, No. 00 Civ. 2843, 2004 U.S. Dist. LEXIS 3104, * 21 (S.D.N.Y. Feb. 27, 2004) ("[T]he opinions of these witnesses on the intent, motives or states of mind of corporations, regulatory agencies and others have no basis in any relevant body of knowledge or expertise.").

Reading documents and drawing inferences about the author's state of mind is not a recognized "expert" methodology. *Rezulin*, 2004 U.S. Dist. LEXIS 3104, at * 23-24 (excluding expert testimony where expert "merely repeated facts or opinions stated by other potential witnesses or in documents produced in discovery … [and] drew simple inferences from documents produced in discovery").

Moreover, even if expert testimony about the state of mind of Abbott or its employees were otherwise admissible, Dr. Fairweather has no personal knowledge or experience to support his speculative assertions as to what Abbott or its employees knew or thought or believed or intended. Dr. Fairweather is not an expert on human psychology or corporate decision-making. *See Lawyers Title Ins. Corp. v. Dearborn Title Corp.*, No. 94 C 3277, 1998 U.S. Dist. LEXIS 3995, * 8 (N.D. Ill. Mar. 30, 1998) (refusing to allow expert to testify as to what a title insurance underwriter did or did not know, or what the underwriter would have done, where the expert had no personal knowledge of what the underwriter believed or what it would have done; expert was also precluded from testifying as to the plaintiff's motivations, since he was not one of plaintiff's employees nor privy to the decision-makers at the company); *Kidder, Peabody & Co. v. IAG Int'l Acceptance Group N.V.*, 14 F. Supp. 2d 391, 398 (S.D.N.Y. 1998) (refusing to allow expert to testify as to the mental processes of the parties in the case, noting that "what they knew, believed, assumed, or understood, on the basis of their own knowledge or communications from others … that evidence must come from the trial testimony of the individuals concerned")

Neither Dr. Fairweather's education nor his experience qualify him to render an expert opinion regarding the mental states of other individuals during the relevant period. *See Sassafras Enters. v. Roshco, Inc.*, 915 F. Supp. 1, 8 (N.D. Ill. 1996) (finding nothing in a business expert's experience that suggests his qualifications as a "mind reader"). Absent any conceivable expert basis for his conclusions about what Abbott allegedly "recognized" (par. 33), "was aware of" (par. 36), "were aware, or should have been aware" (par. 37), "should have recognized" (par. 40), "should have understood" and "knew" (par. 41), and "should have known" (par. 43), Dr. Fairweather is simply acting as an advocate for Hancock's version of the facts. The cases make clear such advocacy cannot be introduced into evidence through "expert" testimony. *See*

Rezulin, 2004 U.S. Dist. LEXIS 3104, at * 21-22 ("[P]laintiffs' experts propose improperly to assume the role of advocates for the plaintiffs' case by arguing as to the intent or motives underlying the conduct of [defendant] or others, a transgression that has resulted in the exclusion of 'expert' testimony as to the 'real motive' behind certain business transactions.") (citing cases).

An expert witness "must be qualified in the specific subject for which his testimony is offered." *Whiting v. Boston Edison Co.*, 891 F. Supp. 12, 24 (D. Mass. 1995) Dr. Fairweather's testimony about the state of mind of Abbott (and the FDA) is merely his own lay opinion based on some (but by no means all) of the same evidence presented to the Court. Because Dr. Fairweather's expertise does not qualify him to opine on the mental state of others, there is nothing in the sections of his affidavit referenced above amounting to expert or scientific knowledge that is "helpful" to the fact finder under Rule 702. The Court should therefore exclude the above-referenced paragraphs of Dr. Fairweather's affidavit concerning the state of mind or motives of Abbott, Abbott's personnel, or the FDA, as well as any testimony concerning these subjects, as unqualified speculation under Rule 702.

3. With respect to the exhibits attached to Dr. Fairweather's affidavit, Abbott incorporates by reference the objections stated in Abbott's Objections to Hancock's Proposed Trial Exhibits, filed January 28, 2008 (as revised).[2]

[2] As noted in Abbott's opposition to Hancock's Motion to Overrule Authenticity and Various Hearsay Objections, Abbott plans to file a revised and narrower set of objections to Hancock's trial exhibits on February 29, 2008. Until such time, Abbott reserves its right to object to exhibits on the grounds stated in its Objections to Hancock's Proposed Trial Exhibits, filed January 28, 2008.

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Dated: February 28, 2008

CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 28, 2008.

Date: February 28, 2008.

/s/ Eric J. Lorenzini

Exhibit A

John Hancock, *et al* v. Abbott Laboratories

Report of

William R. Fairweather, PhD

My Background

My name is William R. Fairweather. I reside at 15405 Narcissus Way, Rockville MD 20853. I am currently self employed as an Expert Regulatory Statistician. My area of expertise is the statistical design and analysis of scientific and medical studies, including clinical trials, which are primarily intended to meet US regulatory requirements for marketing. These studies involve medical devices and biopharmaceutical, biological, and biotechnological products that treat a wide range of diseases and conditions.

I was trained in statistics and mathematics at the University of California, Berkeley (BS, 1964), Cornell University (MS, 1966), and the University of Washington (PhD, 1973). I worked for two years (1968-1970) for the National Heart Institute of the National Institutes of Health. From 1973 to 1998, I worked for the US Food & Drug Administration, Center for Drug Evaluation and Research. I retired from the Food & Drug Administration at the end of 1998 after 25 years of service. I have been a private consultant from 1998 to the present.

FDA Experience

At the FDA, I reviewed the statistical aspects of applications submitted by pharmaceutical companies for marketing approval from 1973 to 1976, when I was made a Group Leader. I became a Branch Chief in 1979 and served as Associate Director of Biostatistics from 1996 to 1998. In brief, my initial responsibility as a reviewer was to determine whether a study design and the statistical analyses submitted by a sponsor were suitable and sufficient to support the claims made by the sponsor for the product. As a Branch Chief, my duties involved supervision of PhD-level statisticians who reviewed pharmacokinetics and biopharmaceutics, animal toxicology, chemistry and manufacturing controls, and post-marketing surveillance studies. My

responsibilities also involved the review of products in AIDS. Later in my career, I was involved in writing and supervising the writing of guidelines intended to help the pharmaceutical industry to understand FDA requirements and to meet these requirements. I participated in the International Conference on Harmonisation which worked to synchronize the regulatory requirements of the United States, Europe and Japan.

I have a number of publications in applied statistics, which are listed on my website (www.flowervalleyconsulting.com). I have also given talks on statistical and regulatory topics at meetings in the US, Great Britain, Italy, Israel, and Belgium. These are also listed in my biography on the website.

The FDA declared me to be an Expert Regulatory Statistician. I also received a number of awards during my service at the FDA including:

- Harvey W. Wiley Medal and FDA Commissioner's Special Citation "for outstanding and sustained application of statistical methodology in the areas of postmarketing risk assessment, carcinogenicity, and animal toxicology with the aim of promoting public health", 1999
- Group Recognition Award for service on Carcinogenicity Assessment Committee, 1997
- Commissioner's Special Citation for service on Tobacco Working Group, 1994
- Commendation for Performance as Acting Division Director, 1991
- US Public Health Service Special Recognition Award, 1987
- Food and Drug Administration Commendable Service Awards, 1980 and 1983
- Food and Drug Administration Award of Merit, 1976

Consultant Experience

As a consultant to industry, I advise on the statistical aspects of scientific and medical studies and clinical trials of all kinds. I also provide statistical designs for these studies, including sample size calculations. I analyze the data of completed studies and compile statistical reports that are included in the sponsor's submission to FDA.

Documents Reviewed

The documents I reviewed for this report are identified in the attached table.

Task

I was asked to assess the available statistical analyses and related reports regarding Abbott Laboratories' clinical trial known as M99-114. I have attempted to determine what a reasonable statistician at a pharmaceutical company such as Abbott Laboratories would know about the status and likely outcome of M99-114 as of 12 March 2001, the day before the agreement was concluded between John Hancock and Abbott Laboratories. My opinion is based on the documents I reviewed, my experience, and on generally accepted statistical theory and practice. In particular, I was asked to focus on the failure of this study to achieve its enrollment target and the likely impact of this failure on the outcome and usefulness of this study.

General Statistical Concepts

In order to understand the issues in this case it is useful to define some of the terms that will occur frequently and the relationships among them. These include Type I and Type II errors, alpha (α), beta (β), and power.

Let's say that a study will compare two groups on some variable (*e.g.*, improvement from baseline on the Likert pain scale). We plan to sample n patients in each group and to compute the mean improvement X_T of patients who received the test product and the mean improvement X_P of patients who received the placebo. In designing the study, we need to determine the sample

size, n. We determine n so as to achieve some particular statistical objective, as described below.

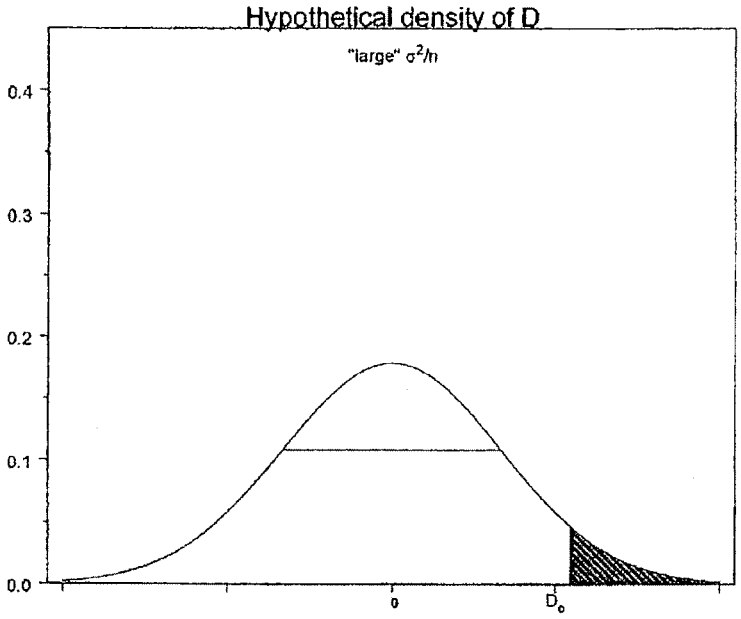
We are interested in the difference $D = X_T - X_P$ because this is an estimate of the true, underlying difference $\delta = \mu_T - \mu_P$ between the treatments. δ (pronounced "delta") is a parameter that can never be fully known; it can only be estimated, for example by D.

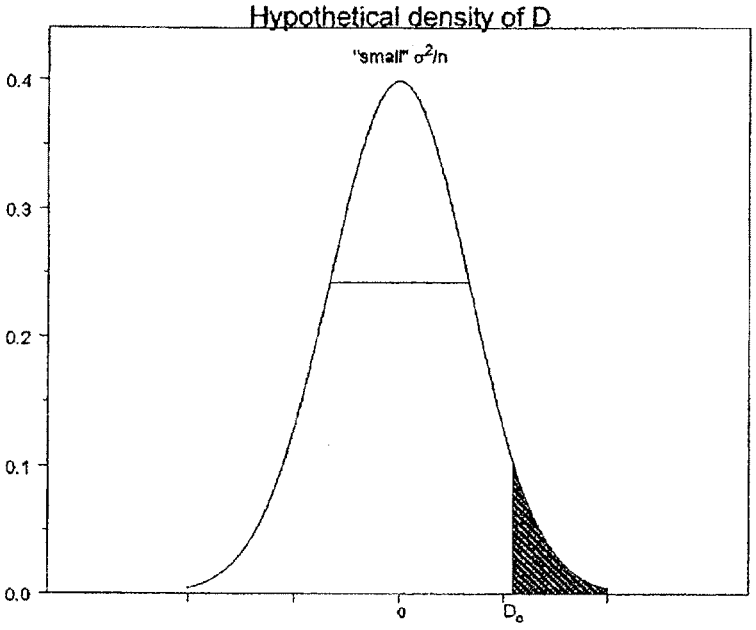
A density function describes the probability that a random variable such as D will take on a particular value or range of values. For planning purposes, we assume that the statistical density of D follows a known formula that depends on δ, n and the variance of the observations σ^2 (pronounced "sigma squared"). The parameters δ and σ^2 are both unknown, but we can use D and the sample variance s^2 to estimate them. n is the sample size in each group.

At the end of the study, we will use a formal test of hypothesis to evaluate whether T is better than P, which corresponds to $\delta = \mu_T - \mu_P$ is greater than zero ($\delta > 0$). We set up the null hypothesis (pronounced "H-naught") to be what we hope is not the true state of affairs:

$$H_o: \delta = 0.$$

We intend that the data will refute this hypothesis. If H_o is true, the statistical density of D is centered at 0. The following graphs describe typical density functions of D, the first for σ^2/n large and the second for σ^2/n small.


Hypothetical density of D
"large" σ^2/n
0.4
0.3
0.2
0.1
0.0
0
D_o


Hypothetical density of D
"small" σ^2/n
0.4
0.3
0.2
0.1
0.0
0
D_o

The length of the horizontal line is a measure of the size of σ^2/n. As we see from the above curves, the smaller σ^2/n is, the more concentrated the curve is about its center point.

The points marked D_c are the "α-critical points" of these two densities. They mark the values of D that have probability α to the right if H_o is true. In summary, the probability that D will be larger than D_c is α. For reasons to be explained below, we wish to limit α. For example, α is typically limited to 5% in pharmaceutical studies.

Note that D_c is not a universal constant; it depends on other parameters of the density. For example, as n gets larger, σ^2/n gets smaller and the value of D_c moves to the left, closer to zero. We can determine the critical value D_c when we know α and σ^2/n.

Returning to the procedure that we will use at the end of the study, we will reject the null hypothesis H_o if $D > D_c$. Then, by the way that D_c is defined, the probability that we will reject H_o is the probability that $D > D_c$. When H_o is true, by design this probability is exactly α. Rejecting H_o when H_o is true is called the Type I error, and our procedure for rejecting H_o based on D_c limits this error to the value α.

The Type I error is the Consumer's Risk. If an ineffective product (T is no better than P) is put onto the market, the consumer suffers. This risk is limited to α.

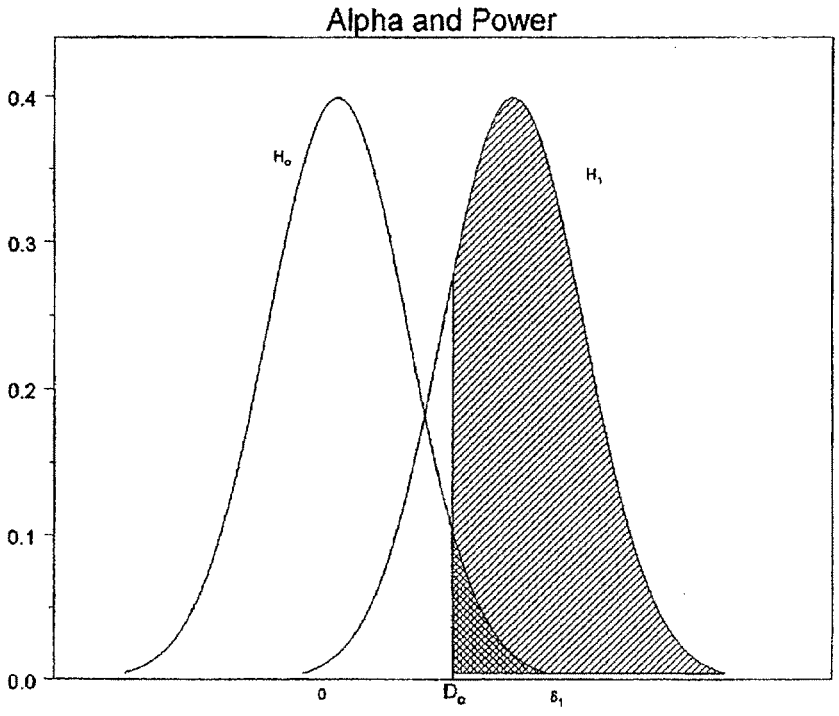
What about the Producer's Risk? If a highly effective product is withheld from the market the producer suffers. This is the Type II error and it is designated β. Statistical power is defined to be $1 - \beta$.

To understand the concept of power fully, we need another hypothesis. This one is called the alternative hypothesis:

H_1: $\delta = \delta_1$ (>0).

δ_1 is the true, unknown effect size. This hypothesis says that the test product mean exceeds the placebo mean by δ_1, indicating that the test product is better than placebo. (Here, δ_1 is positive for the favorable outcome.) If this hypothesis is true, the test statistic would have a higher mean than it has under the null hypothesis (namely, 0). Let's assume for simplicity that σ^2/n is the same under both of these hypotheses.

Drawing the two densities together on one graph allows us to see how the Type I error α and the power $1-\beta$, the shaded regions in the figure, interact. We can also see how to manipulate the figure to achieve the desired power or sample size.



The Type I error, α, is the probability in the area under the H_o curve that is crosshatched. The power, $1-\beta$, is the area under the H_1 curve that is marked by the shading (including the crosshatched area).

Recall that the operating rule is to reject H_o if $D > D_c$ and not to reject H_o otherwise. For the curve on the left (representing the density of D if H_o is true) the amount of probability to the right of D_c is α. For the curve on the right (representing the density of D when H_1 is true) the amount of probability to the left of D_c is β (and to the right of D_c is $1-\beta$).

What happens if δ_1 gets larger? The curve on the right moves further to the right. Consequently, if the amount by which the test is better than placebo increases, D_c and α don't change but β gets smaller (and $1-\beta$ gets bigger).

To determine the power (when σ^2 and n are fixed) we slide the H_1 curve to the right or to the left until it is centered at δ_1. Then power is $1 - \beta$.

We can also use the figure to see how a sample size is determined (for a specified δ_1 and power). If we increase n so that σ^2/n decreases, the two densities become more peaked. The density on the left is still centered at 0, and the one on the right is centered at δ_1. This causes D_c to slide to the left in order to keep α fixed. This can be done until the power is at the desired level. Then we simply note what value of n produced this condition. Of course, in practice this process is accomplished by computer, using mathematical formulas for exact results.

In designing a study, it is desirable to maximize the power to the extent possible to ensure that the study has a very good chance of rejecting the null hypothesis, *i.e.*, of demonstrating that there is an advantage to the test product. As described above, power is increased by decreasing σ^2/n.

This can be accomplished by reducing σ^2 or by increasing n. One way to decrease σ^2 is to measure the study outcome as precisely as possible.

In summary, the power of a statistical analysis is the probability that we will declare the test product to be superior to placebo, when there is a real difference between test and placebo. The numerical amount of the power depends on the amount of the difference and on the inherent variation (σ^2/n) in the comparison.

Adding more patients to the study increases n. On the other hand, if n is reduced the power is also reduced, if all other factors are held fixed.

Summary of Opinion

The following is a brief summary of my opinions in this matter. It is based on the materials that I have reviewed to date. It is subject to modification based on my review of any additional documents or other information.

Relevant Facts Relating to M99-114

In this case, we are interested in the ramifications of the failure of a study that was terminated by Abbott Laboratories before it reached the planned patient enrollment. The statistical ramifications are clear. The power calculation shows how many patients are needed to give a desired level of power 1-β when the difference δ_1 between the test product and the placebo is specified, and when the population variance σ^2 is specified. In this case, the difference was specified to be 0.46 and n was calculated to be 80 patients for each of the four arms of the study, for a total of 320 patients. Stopping the enrollment prematurely can only reduce the power to detect this presumed difference between the test and placebo means, if all other factors remain the same.

The study under discussion was conducted under protocol M99-114, titled "M99-114: A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-

594 to Placebo in Subjects with Painful Diabetic Neuropathy" (ABBT65818 to ABBT65896, dated 2/8/00). This study was initiated in April 2000 and was scheduled to end in June 2001 with 320 patients enrolled (ABBT246082, dated February 2001). The blind was broken on 4/23/01 (ABBT79395, Email 3/8/02) and the study report was dated 7/31/01 (ABBT241331 to ABBT241560, Analysis dated 7/31/01).

In one Abbott document (ABBT159274, Email dated 9/3/99), it was noted that an earlier Phase II study in osteoarthritis patients used 50 mcg and 75 mcg doses without titration (slow increase in dose to allow the patient to get used to the drug). It was suggested that for neuropathic pain, titration to higher doses would be needed in order to show efficacy. M99-114 used placebo and three doses of ABT-594: 150 mcg BID, 225 mcg BID, and 300 mcg BID (ABBT65818 to ABBT65896, Protocol dated 2/8/00). Titration was employed, and the titration schedule is reproduced below (ABBT65847, Protocol dated 2/8/00).

Eighty (80) patients were to be enrolled in each of the four dose groups in order "... to allow for the detection of a 0.46 effect size in the average Daily Pain Intensity score for change from baseline to the final evaluation between any ABT-594 treatment group and placebo at 0.05 (two-tailed Type I error) level with at least 80% power." Data from previous studies were used to determine the parameters that went into this calculation (ABBT159274, Email dated 12/21/99).

From the documents that I reviewed, it is clear that Abbott staff were tracking, analyzing, and discussing the enrollment and retention of patients, at least from 5/31/00 onward (ABBT33472 to ABBT33467, Email dated 5/31/00). There appears to have been concern about the rate of enrollment, at least from 5/25/00, when in a letter to one of the investigators, Ms. Collicott indicated that the site would be terminated for slow enrollment (ABBT242154, dated 5/25/00).

In addition, there was concern about retention from at least from 7/7/00, when Dr. McCarthy wrote that of 78 patients enrolled, 31 had already terminated, 20 of whom terminated for adverse

events known to be associated with the drug. The known day of termination (after enrollment) was used by Dr. McCarthy to postulate that the patient could have been in the dose titration phase and would then be receiving 150 mcg, 225 mcg or 300 mcg BID, depending on the day of termination (ABBT82516, Email dated 7/7/00).

The titration schedule of the study is shown below. Dosing on Day 1 was once per day and thereafter was twice per day. On Days 1-3 all patients received 75 mcg; on Days 4-5 they all received 150 mcg. On Days 6-7 patients who were randomized to higher doses were given 225 mcg and those randomized to 150 mcg remained at that dose. Day 8 was the first day of the treatment period and every patient received the dose to which he or she was randomized. Due to the possibility that the adverse events were drug related, and to assuage investigator concerns in this area, Dr. McCarthy proposed to eliminate the 300 mcg BID dose (ABBT82516, Email dated 7/7/00).

The minutes of the Pain Strategy Decision Analysis meeting that took place on 3/5/01 indicate that, based on the available preliminary data, the attendees recognized that tolerability of ABT-594 was an issue of concern (ABBT298380). This appears to be a concept meeting to lay out the issues to be addressed in subsequent analyses of the study data.

Although there were several documents that indicated that the 300 mcg group would be terminated while the M99-114 study was under way, I found no document that indicated that the group was, in fact, terminated. Instead, it is clear that enrollment into protocol M99-114 was stopped as of 1/5/01 (ABBT233539 to ABBT233540, Email dated 12/14/00). Moreover, at some point senior management at Abbott were apparently considering the termination of ABT 594, not merely the M99-114 study. At the time the Initial Portfolio Prioritization was written, ABT 594 was marked "P(ending), awaiting results from ongoing P(hase) II trial—probably T(erminate)", with timing for June or July (ABBT155584, Initial Portfolio Prioritization).

The tracking of enrollment and premature terminations around this time (ABBT238329 to ABBT238333, Email dated 2/27/01) would have indicated that the usable sample size would be only 137 patients (269 enrolled less 132 terminated), not the 320 planned.

Conclusion

By 12 March 2001 I believe that Abbott's statistical staff were, or should have been, aware that the M99-114 study would be substantially underpowered to reach its objective. They could easily calculate the available power; indeed, power for various sample sizes had already been calculated (ABBT80232 to ABBT80237, Email dated 8/29/00). In the highly unlikely event that all of the available patients had been divided equally between the placebo group and one other ABT-594 group (*e.g.*, 150 mcg, 225 mcg, or 300 mcg group), resulting in the maximum possible power under the circumstances, Abbott's own power curves would indicate the power for 69 patients per group would still be less than 75%, *i.e.*, below the target 80% power.

If, in the more likely scenario, the 137 available patients had been distributed evenly across the dose groups, with approximately 34 in each group, the power would have been less than 50% (ABBT80232 to ABBT80237, Email dated 8/29/00). That is, the probability of M99-114 to declare that the test product was superior to placebo would be less than the toss of a fair coin.

The actual power would depend on the distribution of these patients among the dose groups, but it would fall between these two values. That is, as of 12 March 2001, it would seem most likely that M99-114 would have difficulty observing a statistically significant treatment effect and was, therefore, likely to be a failed study. In addition, the large proportion of premature terminations implies that the product could not be tolerated in its current formulation. Indeed, other formulations, including enteric coated oral, patch, depot dosage forms, sublingual/buccal, parenteral, intrathecal, and intranasal were already being considered by Abbott before 13 March 2001 (ABBT298380 to ABBT298385, Meeting Minutes 3/5/01).

I did not see any evidence in the documents that I reviewed that would indicate that there was another ongoing study that would have supported a Phase III study of ABT-594. That is, a successful conclusion to M99-114, demonstrating a statistically significant efficacy finding, preferably one not clouded by substantial adverse events, was essential to provide the cumulative scientific evidence that would justify undertaking a Phase III study.

From my experience at the FDA, and my review of the documents as of 12 March 2001, it is my opinion that the statisticians at a reasonable pharmaceutical company, such as Abbott Laboratories, would realize that ABT 594 would face serious questions that might, at the very least, delay or prevent its entry into Phase III.

William R Fairweather

William R. Fairweather, PhD

19 January 2007

Date

Table 9.4.1a ABT-594 Dose Escalation

Treatment Regimen	Suggested Dosing Time	Days 1-7						
		1	2	3	4	5	6	7
150 µg ABT-594	8 AM	[redacted]	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg
225 µg ABT-594	8 AM	[redacted]	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg
300 µg ABT-594	8 AM	[redacted]	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg

Subjects will start study drug at PM dose on Day 1 (Section 9.4.5).

The number and type of HGCs per dose for the Treatment Phase is presented in Table 9.4.1b.

Table 9.4.1b Number and Type of Capsules by Treatment Regimen

Treatment Regimen	Number of Capsules Per Dose (Days 8-49)	
	Daily Blister Card (BID dose)	
	75 µg ABT-594 HGC	Placebo ABT-594 HGC
ABT-594 150 µg	2	2
ABT-594 225 µg	3	1
ABT-594 300 µg	4	0
Placebo	0	4

Documents reviewed for this statement

Abbott #			
From	To	Date	Description
159274		09/03/99	Email to Waleska from Silber
51889		12/21/99	Email to Siebert from Thomas
65818	65896	02/08/00	Protocol M99-114
242154		05/25/00	Letter to Hoffstetter from Collicott
33462	33467	05/31/00	Site breakdown/enrollment for M99-114
79825		06/20/00	Emails between Nunn and Thomas
241296		06/27/00	Emails among McCoy, Rowbotham and Collicott re barriers to enrollment
161395		07/06/00	Email to Matalonis, et al from Garavalia
82516		07/07/00	Email to Morris, et al from McCarthy
239985	239988	07/10/00	Site breakdown/enrollment for M99-114
83022		07/13/00	Email to Landsberg, et al from Collicott
161644	161645	07/25/00	Emails among Biarnesen and Powers
78935	78941	08/07/00	Email to Thomas from Hansen with patient listing
335227	335307	08/23/00	ABT-594 Development Plan
80232	80237	08/29/00	Email to Kacos from Thomas with data for power curves
241302		08/31/00	Letter prototype to investigators from Collicott
51907	51908	09/28/00	Power calculations
82259		09/28/00	Email to Brown from Thomas with power calculations
51892	51905	09/28/00	Email to Brown from Thomas with power calculations
233741	233749	09/28/00	CT Recruitment and Centralized Screening Program
237155	237159	10/09/00	Email to Nunn from Collicott with investigator tracking list
107607	107609	10/30/00	Email to Biarnesen from Silber with list of project review questions
109399	109400	11/22/00	Email to Morris from McCarthy with items for meeting discussion
241843	241847	11/28/00	Email to Schanzenbach from Collicott
81606		11/29/00	Email to Kacos from Thomas with confidence intervals for difference
242373		12/06/00	Email to Biarnesen from Collicott re randomization goals
233539	233540	12/14/00	Email to Schanzenbach from Collicott "decided to end enrollment as of 1/5/01"
240624		01/08/01	Email to Schanzenbach from Collicott
81459	81460	01/12/01	Email to McCarthy from Thomas with adverse event experience
233000		01/15/01	Email to Schanzenbach from Collicott
242694	242698	01/16/01	Meeting agenda with tables of investigators and early terminations
242693	242699	01/16/01	Meeting agenda with tables of investigators and early terminations
8165	8173	Feb 2001	Descriptive memo on marketing prospects
246076	246084	Feb 2001	Descriptive memo on marketing prospects
242650		02/05/01	Tracking report
242653		02/12/01	Tracking report
242682	242686	02/13/01	Meeting agenda with tables of investigators and early terminations
237944		02/20/01	Tracking report
233001		02/26/01	Tracking report
238329	238333	02/27/01	Meeting handouts with tables of investigators and early terminations
298380	298385	03/05/01	Meeting minutes: Pain Strategy Decision Analysis
297530	297555	03/07/01	Abbott Portfolio Review
238328		03/13/01	Tracking report
8078	8211	03/13/01	Research Funding Agreement by Hancock and Abbott
240978		03/20/01	Tracking report

79111	79118	05/23/01	Adverse event experience tables
241331	241560	07/31/01	M99-114 Analysis
241298	241300	08/14/01	Study enrollment graphs
80451		02/19/02	Email to Olson from Thomas "screening failure rate 47%"
79395		03/06/02	Email to Biarnesen from Thomas indicating blind broken 4/23/01
51885	51888	???	Power curves
155581	155587	???	Initial Portfolio Prioritization

Exhibit B

UNITED STATES DISTRICT COURT

DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, et al Plaintiff	:	Civil Action No. 05-11150-DPW
V.	:	Courtroom No. 1
	:	1 Courthouse Way
	:	Boston, MA 02210
ABBOTT LABORATORIES, Defendant	:	2:30 p.m., Thursday October 25, 2007

Pretrial Conference

Before: THE HONORABLE DOUGLAS P. WOODLOCK,
UNITED STATES DISTRICT JUDGE

APPEARANCES:

Choate, Hall & Stewart, (by Brian A. Davis, Esq., Karen C. Troake, Esq., and Joseph H. Zwicker, Esq.) Two International Place, Boston, MA 02110, on behalf of the Plaintiffs.

Griesinger, Tighe & Maffei, LLP, (by Andrew C. Griesinger, Esq.) 176 Federal Street, Boston, MA 02110-2214, on behalf of the StoneTurn Group, LLP.

Donnelly, Conroy & Gelhaar, LLP, (by Michael S. D'Orsi, Esq.), One Beacon Street, 33rd Floor, Boston, MA 02108, on behalf of the Defendant, Abbott Laboratories.

Munger Tolles & Olson, (by Jeffrey I. Weinberger, Esq.) 335 South Grand Ave. - Suite 3500, Los Angeles, CA 90071-1560, on behalf of the Defendant, Abbott Laboratories.

Eric J. Lorenzini, Esq. 444 N. Sierra Bonita Ave., Los Angeles, CA 90036, on behalf of the Defendant, Abbott Laboratories.

that's going to be meaningful.

Mr. Tucker, if what we're talking about here is something that is -- on the piece with Mr. Friedman's role as a damage expert, if you're talking about a Daubert challenge or something like that, I'm not sure it's going to be particularly forceful for me.

These are your experts. They seem to be people -- although I haven't spoken to Mr. Tucker -- they seem to be people of substance. I would want to look at their testimony and make my own decision about it.

So, the idea of motions in limine strikes me as not a useful deployment of resources to deal with that. I think it's probably going to be -- unless there is something about Mr. Tucker that, you know, says that he's also an expert in, say, coffee makers and toasters, kind of an all-purpose expert and consequently not worth my thinking about, I suspect I'll listen to what he has to say.

So, you think about whether or not you want to make such a motion. But, it doesn't strike me on its face as being particularly helpful, particularly useful for the parties to pursue.

I'm not sure I understand precisely what additional opinions we're talking about here and you're

not sure about that either.

MR. DAVIS: No, your Honor. There's a little bit of a discontinuity here because the expert reports were due last October, when discovery was still underway, because of a variety of extensions.

THE COURT: Right.

MR. DAVIS: So, at some point in time we do want to reconcile so that experts aren't -- for example, Mr. Friedman's report was issued in October of 2006. There've been a number of depositions that have been taken since that time. He will want to have reviewed those.

THE COURT: Well, okay. Let me take it in the broader sense, which is to bring this to rest. And so, at some point, experts have to be in a position to say: This is where I now stand, having thought about it, in light of deposition discovery, and that sort of thing. That doesn't mean expanding on those opinions, but it will be final to both sides.

So, do you want a date?

MR. DAVIS: Yes.

THE COURT: What date?

MR. DAVIS: December 1.

THE COURT: Is that a reasonable date?

MR. WEINBERGER: Well, your Honor, all of the

-- the fact that depositions were done before we did expert discovery --

THE COURT: Well, I understand that.

But, what happened -- I mean, you know --

MR. DAVIS: No, they weren't.

THE COURT: The reason that your -- why this is a high-maintenance case is that money appears to be no object. In lower-maintenance cases in which money is an object, I try to tighten up more recognizing that every time a deposition is taken that an expert rethinks what they think.

I want this -- I want you to have had an opportunity to explore what the expert thinks, but, ultimately, I want an expert opinion, which is going to be in the affidavit, in the form of the affidavit, ultimately, to be the one that the expert is prepared to stand on at that point.

Now, what that means for me is that the expert doesn't all of a sudden start offering opinions on some new issue or some broader issue, but they can refine their reports so that you know what his last -- or her last and best offer is about testimony.

MR. WEINBERGER: I guess, your Honor, I don't have a problem with experts permitted to update his reports to reflect any depositions that were taken after

this. But, what I do have a problem with is all of a sudden having all kinds of new opinions that could have been made before. We have no right -- ability to take discovery.

THE COURT: I agree.

MR. DAVIS: And, I do as well.

THE COURT: Okay.

So, we'll use the December 1 date for the submission of the final expert reports which will be simply refinements and not expansions of the opinions that they rendered within the discovery period.

Now, the unreliability of Mr. Fairweather. I don't know what to say about it. But, I understand that somebody is concerned about this. But, is this the time to talk about it?

MR. WEINBERGER: Well, your Honor, I -- this is -- obviously, it's not a jury trial. This is clearly a motion we would bring in a jury situation. If the Court's preference is to, as with the damages, to wait and to hear it and then to decide and move either in the middle of the trial or the end, we have no problem with that.

We wanted to put the Court on notice that we have serious scientific problems with this opinion.

THE COURT: Well, I think that my view, I

THE COURT: All right. Thank you very much.

THE CLERK: All rise.

(Whereupon the hearing was concluded.)

CERTIFICATE

I, Marie L. Cloonan, Official Reporter of the United States District Court, do hereby certify that the foregoing transcript, from Page 1 to Page 62, constitutes to the best of my skill and ability a true and accurate transcription of my stenotype notes taken in the matter of Civil Action No. 05-11510-DPW, John Hancock Life Insurance Company, et al v. Abbott Laboratories.

Marie L. Cloonan

Official Court Reporter